MINIREVIEW

Treatment of Q Fever

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INTRODUCTION

Q fever is a widespread disease caused by *Coxiella burnetii* (17). The disease is very protean, and its prevalence in many parts of the world is unknown since prospective studies have not been carried out. In regard to antibiotic therapy, two major problems are of concern. First, clinical evaluation is difficult because acute Q fever is usually diagnosed retrospectively and is usually a self-limited disease. Moreover, evaluation of therapeutic success in chronic Q fever requires prolonged follow-up because of the possibility of late relapses. Second the experimental evaluation of antibiotic therapy is problematic because *C. burnetii* is a strict intracellular pathogen and no animal model of chronic infection has been successfully described so far.

THE BACTERIUM

C. burnetii is a strict intracellular gram-negative bacterium. It lives and multiplies in the phagolysosomes of infected cells at pH 4.8 (9). Thus, in order to be active, an antibiotic compound should enter the cell, concentrate within the lysosome, and be active at pH 5 or less (18, 26). *C. burnetii* in culture has a phase variation (phases I and II) (35) equivalent to the lipopolysaccharide smooth-rough phase variation of members of the family *Enterobacteriaceae*. Phase I cells, but not phase II cells, are infectious, and the serological response of patients with acute Q fever is mainly directed against the phase II cells. *C. burnetii* also has a spore-like cycle (20) which allows resistance to heat and disinfection. Several genotypes of *C. burnetii* exist, and it has been hypothesized that some strains cause acute Q fever and others cause chronic Q fever (15).

THE DISEASE

Q fever is a disease with protean manifestations; when exposed to an aerosol, a human being could have an asymptomatic seroconversion (in one-half of cases [5]) or symptomatic acute Q fever. The disease is usually mild and self-limited. In a recent Swiss outbreak, 4% of seroconvertors were hospitalized (5). With a series of 323 hospitalized patients, my colleagues and I recently showed that one-third presented with clinically isolated fever, two-thirds presented with increased hepatic enzymes, one-half presented with pneumonitis, one-fifth presented with cutaneous lesions, and one-tenth presented with neurological symptoms; the lethality was 2.4% (37).

Chronic Q fever, in our experience with a series of 92 patients, was diagnosed in patients with preexisting heart (54 cases) or vascular (6 cases) disease and/or an immunocompromising situation (17 cases). The clinical spectrum included endocarditis (two-thirds of the cases, in one-fourth of

which the patient died), infection of vascular aneurysm (three cases) or prosthesis (three cases), osteomyelitis (three cases), lung infections (pseudotumor of the lung [one case] and fibrosis [three cases]), and hepatitis (three cases) (3).

In chronic Q fever, there is an absence of cellular immune response to *C. burnetii* associated with a very high antibody response to both phase I and phase II of the bacterium (21). As determined by microimmunofluorescence, an anti-phase I immunoglobulin G (IgG) antibody titer of $\geq 1/800$ and an IgA titer of ≥ 100 indicate chronic infection (21, 28). By complement fixation, a titer of $\geq 1/200$ for phase I is diagnostic for chronic Q fever.

EVALUATION OF ANTIBIOTIC SUSCEPTIBILITY

C. burnetii does not multiply in axenic medium, and three models of infections for antibiotic testing have been used: animals, embryonated eggs, and cell cultures.

Animal model. Guinea pigs were used first to test streptomycin, which was demonstrated to be efficient at doses which were not suitable for humans because of toxicity (11).

Embryonated eggs. Embryonated eggs represent a good model of infection for testing the bacteriostatic activity of antibiotics. Antibiotics are injected via the yolk sac just after inoculation, and the prolongation of the mean survival time determines the antibiotic efficacy. It has been demonstrated that tetracyclines and analogs, co-trimoxazole, and rifampin (29, 34) are effective in this model, but none was bactericidal. Penicillin, cephalothin, streptomycin, chloramphenicol, clindamycin, and erythromycin were not bacteriostatic (34), and one of the tested strains (Cyprus strain) was resistant to tetracycline (34).

Cell culture. The therapeutic goals for acute Q fever and chronic Q fever are different; i.e., in acute Q fever a bacteriostatic effect is sufficient to help the patient recover, but in chronic Q fever a bacteriostatic regimen may allow disease control but will not cure the patient. In this setting a bactericidal regimen seems necessary. We developed two models of cell culture to determine the bacteriostatic and the bactericidal effects of antibiotics.

For assessment of the bacteriostatic effect, we described a shell vial assay using HEL cells, which made it possible to determine the susceptibilities of 13 strains of *C. burnetii* to antibiotics (27). In this model, tested strains could be considered resistant, susceptible, or of intermediate susceptibility (when the multiplication is slower than in controls but not stopped). By this model, amikacin and amoxillin were never effective. Co-trimoxazole, rifampin, doxycycline, tetracycline, and minocycline (27), sparfloxacin (25), and the quinolones PD 127,391 and PD 131,628 (12) were always active. Of 13 cases, strains were susceptible to ofloxacin in 12, to pefloxacin in 10, and to chloramphenicol in 10 (27) and to

ceftriaxone in 4 and to fusidic acid in 6 (39). For erythromycin 7 of 13 strains were of intermediate susceptibility and 6 were resistant (27).

For chronic infection, a model of persistently infected cells was developed first by Yeaman et al. (29, 46); in this model cells and bacteria grew simultaneously. We used this model (24, 29) and then demonstrated that it was not evaluating bactericidal activity because of the bias of cell multiplication, which diluted bacteria. We showed that blocking cell multiplication made it clear that no antibiotic compound was bactericidal (26). Later we introduced a more sophisticated model using P388 (a murine macrophage cell line), in which we compared the number of live bacteria after 24 h of incubation of the initial inoculum with antibiotics. Using this technique, we demonstrated that pefloxacin, doxycycline, ciprofloxacin, and rifampin were not bactericidal (18). We also tested clofazimine, pirazinamide, and minocycline, which were ineffective as well (19). Because *C. burnetii* lives in an acidic environment (9) we speculated that the low pH inhibited the antibiotic bactericidal activity. Using amantadine, chloroquine, or NH_4Cl, we were able to increase the lysosomal pH to, respectively, 5.3, 5.7, and 6.8. When antibiotics were added, rifampin was still not bactericidal, doxycyline became bactericidal at pH 5.7 and 6.8, and pefloxacin became bactericidal at pH 6.8. We concluded from this work that pH was critical for antibiotic efficacy for *C. burnetii* and that a bactericidal regimen should include either a lysosomotropic alkalinizing agent or an acid-stable antibiotic (18).

MEDICAL TREATMENT OF ACUTE Q FEVER

The treatment of acute Q fever depends on the clinical presentation; pneumonia usually resolves without treatment within 15 days. Clinical evaluation of the efficacy of antibiotic regimens is difficult because of the short duration of the disease as well as the late confirmation of the serological diagnosis. Because of this, uncontrolled studies are of little value. A randomized study has been carried out with tetracycline alone, which reduced the duration of fever by 50% (23). However, treatment must be started within the first 3 days of illness to be effective. Thus, empiric therapy appears to be justified in severely ill patients, as serological diagnosis is not available at that time.

In a nonrandomized comparison of two regimens of acute Q fever treatment, the average duration of fever was 3.3 days in untreated patients, 2 days in patients receiving tetracycline (500 mg four times a day), and 1.7 days in those treated with doxycycline (100 mg four times a day) (33). Thus, doxycycline was superior to tetracycline, which was superior to the placebo. Ofloxacin (600 mg/day) and pefloxacin (800 mg/day) were reported to be effective in Q fever pneumonia, producing apyrexia and clinical improvement 2 to 4 days after establishment of chemotherapy (2). However, antibiotic treatment was prolonged for 16 days with ofloxacin and 21 days with pefloxacin. The combination of pefloxacin (800 mg/day) and rifampin (1,200 mg/day) for 21 days successfully treated patients with prolonged Q fever. Although these patients received antibiotic treatment from 11 to 36 days after the start of the illness, all of them recovered. Erythromycin has been used to treat pneumonia caused by *C. burnetii* (22). Patients who had community-acquired pneumonia and were receiving various antibiotic regimens were evaluated. Those with acute Q fever pneumonia who received erythromycin had a rapid clinical improvement with apyrexia by day 4. Patients treated with beta-lactams

did not improve, but apyrexia and clinical improvement were achieved when the antibiotic treatment was changed to erythromycin. However, erythromycin was reported by Marrie to be ineffective in severe cases of Q fever pneumonia despite use of a daily dosage of 4 g (17). Whether erythromycin is an adequate treatment for atypical pneumonia, when Q fever is considered as a possible diagnosis, has yet to be confirmed. Discrepancies among series could be related to the heterogeneity of antibiotic susceptibility among strains, as demonstrated in vitro (27). Other antibiotics, such as chloramphenicol, co-trimoxazole, and ceftriaxone, have been reported to be effective in acute Q fever (39, 45).

However, tetracycline compounds and especially doxycycline are still the drugs currently recommended to treat acute Q fever illness. A regimen of doxycycline at 200 mg for 15 to 21 days is usually prescribed. Quinolone compounds should be considered for Q fever meningoencephalitis, as they penetrate the cerebrospinal fluid (4).

With hepatitis, Q fever is often associated with a strong immune response, including autoantibodies directed against smooth muscle and antinuclear antibodies or a positive Coombs test (13, 16). In this case antibiotics could fail to completely resolve symptoms, and anecdotical reports mentioned the clinical benefit of 40 mg of prednisone daily for 7 days (13).

ANTIBIOTIC AND SURGICAL TREATMENT OF CHRONIC Q FEVER

Q fever endocarditis is the most serious complication of *C. burnetii* infection. More than 200 documented cases of this form have been described, and mortality rates can exceed 65% (1, 3, 6, 10, 31, 32, 36, 38, 43, 44).

Although various regimens have been proposed, tetracycline is the mainstay of treatment of Q fever endocarditis (6, 41, 44). Prescribed alone, it seems to improve the medical condition of patients as long as it is given (44). However, recovery of viable *C. burnetii* from valve tissue has been reported after 4 years of therapy with doxycycline (41). Therefore, doxycycline alone was found to be unable to cure *C. burnetii* endocarditis, and combination antibiotic therapy was proposed. Historically, lincomycin was the first drug to be added to tetracycline (42); thereafter co-trimoxazole was added to either tetracycline or rifampin (36). Co-trimoxazole has been proposed for treatment of *C. burnetii* infection. Alone, it failed to cure Q fever endocarditis despite 31 months of treatment (38). Results obtained with combinations including co-trimoxazole are still controversial. Reports (7, 8, 10, 36, 43) show that among nine patients requiring valve replacement and receiving therapies of various durations including co-trimoxazole, viable *C. burnetii* was recovered from six. One patient was treated with co-trimoxazole combined with doxycycline and died 30 months after initiation of therapy. Therefore, antibiotic combinations including co-trimoxazole may not be the best treatment for Q fever endocarditis (14). The beta-lactams used either alone or in combination with aminoglycosides are not effective (27, 48).

Rifampin combined with either doxycycline or co-trimoxazole has been used in treating Q fever endocarditis, with apparent efficacy. However, in most cases, rifampin treatment was stopped after few months because of its interactions with anticoagulants frequently prescribed at the same time.

The in vitro efficiency of fluoroquinolones against *C.*

burnetii (46) led us to prescribe combinations of doxycycline and either pefloxacin or ofloxacin in 16 cases (14). The mortality rate of these 16 patients was significantly lower than that of patients treated with other antibiotic regimens. In two cases, viable *C. burnetii* was isolated from excised valves, despite 9 and 12 months of treatment. This fact is in contradiction with the reported in vitro bactericidal effects of quinolones (47) but is in accordance with the new model of infection that we described, which shows that these compounds are bacteriostatic (30). The in vitro efficacy of fluoroquinolones combined with rifampin has been recently reported (48), but no clinical data are available. Valve replacement was proposed in addition to antibiotic treatment in cases of Q fever endocarditis (7). In our study, cardiac surgery was performed on 19 patients with hemodynamic failure. When possible, valve tissue was cultured, and *C. burnetii* was isolated in nine cases. A second valve replacement was performed for a patient, 1 year after the first one, and the culture was again positive. Surgery must be accompanied by antibiotic therapy to prevent reinfection from a dormant site, including the other cardiac valves. In fact, *C. burnetii* has been observed in valves which were macroscopically unremarkable (10). Thus, the ideal duration of treatment is difficult to define since no criteria for a cure have been proposed at this time; suggestions range from 1 year (44) to indefinite administration (40). The occurrence of relapse is unpredictable. Our serological data, the fact that positive cultures were obtained after 1 year of treatment, and the possibility of dormant sites with risk of relapse led us to advise a minimum of 3 years of treatment. Relapses are frequent despite prolonged antimicrobial chemotherapy, and the mortality rate can exceed 60% (36). We follow patients with chronic Q fever, and we determine antibody levels every 3 months by using microimmunofluorescence. At the time of diagnosis, IgG and IgA antibody titers range from 1/800 to 1/2,000,000. The decrease of antibodies under specific therapy is very slow, and in some patients the antibody titers stay at a plateau. We consider that no anti-phase I IgA and an anti-phase I IgG titer of ≤1/200 indicate a definite cure. In our experience, this never happens within 3 years of currently recognized treatment.

In conclusion, some aspects of the therapy should be stressed. (i) Currently, no treatment, not even combined antibiotic therapy that includes fluoroquinolones, is capable of eradicating Q fever endocarditis within 2 years. (ii) No treatment can cause titers of IgG antibodies against phase I antigen to drop below 400 within 2 years. (iii) *C. burnetii* remains in valve tissue or in dormant sites despite 2 years of antibiotic treatment. This observation could explain the risk of relapse a few years after treatment. Thus, we recommend that Q fever endocarditis be treated for a strict minimum of 3 years with a combination of doxycycline and a fluoroquinolone. Valve replacement should be reserved for hemodynamic failure. After 3 years, treatment could be stopped if the level of IgG against phase I antigens is still below 400 and no IgA against phase I is detectable.

THERAPEUTIC PERSPECTIVES

We are currently studying an antibiotic regimen combining 900 mg of chloroquine per day with 200 mg of doxycycline per day on the basis of the fact that in vitro 1 μg of chloroquine per ml makes doxycycline bactericidal against intracellular organisms. Twenty patients are currently being treated with this regimen. Preliminary results show that this treatment is amazingly efficient, with some patients being cured by 1 year of therapy, but more definitive results are not available because of the short follow-up.

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